Amendments to the specification:

Please replace the paragraph on page 1, lines 4-13, with the following:

RELATED APPLICATIONS

Benefit of priority under 35 U.S.C. §119(e) is claimed to U.S. provisional application Serial No. 60/394,347, filed July 2, 2002, to Edwin L. Madison, Edgar O. Ong and Juinn-Chern Yeh, entitled "NUCLEIC ACID MOLECULES ENCODING SERINE PROTEASE 16, THE ENCODED PROTEINS AND METHODS BASED THEREON." The subject matter of [[each of]] the provisional application and International PCT application No. ~~Docket No. 24745-1625PC,~~ PCT/US03/20959 filed on the same day herewith, entitled "NUCLEIC ACID MOLECULES ENCODING SERINE PROTEASE 16, THE ENCODED POLYPEPTIDES AND METHODS BASED THEREON", is incorporated by reference in [[it]] its entirety.

Please replace the paragraph on page 5, line 27 through page 6, line 6, with the following:

Provided herein are proteins designated CVSP16 and protease domains thereof. CVSP16 is a member of the serine protease family and is expressed or active in breast, colon, lung, prostate, kidney, stomach, spleen, thyroid gland, trachea and pituitary gland and in tumor tissues and cancers, including colon, breast and prostate cancers, and in leukemias and lymphomas. Hence, as a protease it can be involved in tumor progression. By virtue of its functional activity it can be a therapeutic or diagnostic target. The expression and/or activation (or reduction in level of expression or activation) of the expressed protein (zymogen) ~~of the this protein~~ can be used to monitor cancer and cancer therapy.

Please replace the paragraph on page 6, lines 17-30, with the following:

CVSP16 polypeptide is expressed as a secreted protein and may bind to cell surface receptors to function as a cell-surface bound protease, such as by binding thereto or by dimerization or multimerization with a membrane-bound or receptor-bound protein. CVSP16 polypeptides are serine proteases and exhibit catalytic activity and also can exhibit substrate and ligand binding activity. The CVSP16 proteases provided herein do not include a contiguous sequence of ~~at 5 least~~ at least five amino acids from SEQ ID No. 21 inserted between residues corresponding to Q_{660} and M_{661} and/or the CVSP16 proteases ~~contains~~ contain at least two protease domains of a serine protease 16 (CVSP16) and ~~includes~~ include at least 5 contiguous amino acids corresponding to residues 508-544 of SEQ ID No. 6[[.]] or ~~contains~~ contain the contiguous sequence Asn Asp Ser or Trp Asn Asp or Ser Cys Trp Asn Asp Ser or Cys Trp Asn Asp Ser or Gln Thr His or Leu Gln Thr His in the second protease domain.

Please replace the paragraph on page 7, lines 13-27, with the following:

In addition CVSP16 has a second protease domain PD2, in which the catalytic histidine is replaced by a serine, indicating that the second protease domain has lower catalytic activity. The isolated protease domains as single chains are provided as are polypeptides that include such protease domains. In particular, a polypeptide that contains PD1 as the only CVSP16 portion is provided. Also provided are ~~polypeptides~~ polypeptides that include PD1 and/or PD2, but do not include at least 5 contiguous amino acids from SEQ ID No. 21 and polypeptides that include PD1 or PD2, particularly polypeptides that include PD1 and/or PD2 as the only CVSP16 portion. Also included are CVSP16 proteases that contain at least two protease domains of a serine protease 16 (CVSP16) and include at least 5 contiguous amino acids corresponding to residues 508-544 of SEQ ID No. 6[[.]] or ~~contains~~ contain the contiguous sequence Asn Asp Ser or Trp Asn Asp or Ser Cys Trp Asn Asp Ser or Cys Trp Asn Asp Ser or Gln Thr His or Leu Gln Thr His in the second protease domain.

Please replace the paragraph on page 7, line 28 through page 8, line 2, with the following:

Isolated PD1 and/or PD2 are provided as single-chain molecules [[are]] and as activated one, two or three chain molecules. Each of PD1 or PD2 can exhibit functional activity (catalytic, substrate binding and/or ligand binding activity) without undergoing activation cleavage and/or as single chains.

Please replace the paragraph on page 8, lines 13-25, with the following:

Such assays are also provided herein. In exemplary assays, the effects of test compounds on the ability of the full-length[[-]] single chain, multiple chain activated forms, or a protease domain, which is a single chain or a double chain activated form, of CVSP16 to proteolytically cleave a known substrate, typically a fluorescently, chromogenically or otherwise detectably labeled substrate, are assessed. Agents, generally compounds, particularly small molecules, that modulate an activity of the polypeptide (full length or protease domain(s) either single or double chain or multi-chain forms thereof) are candidate compounds for modulating an activity of a CVSP16. The protease domains and full length proteins also can be used to produce antibodies that bind to CVSP16s provided herein as well as single-chain protease-specific antibodies and/or multi-chain specific antibodies.

Please replace the paragraph on page 9, line 27 through page 10, line 8, with the following:

As noted, the nucleic acid and amino acid sequences of an exemplary CVSP16 are set forth in SEQ ID Nos. 5 and 6. Molecules with single or a plurality of amino acids insertions, deletions or substitutions are ~~provides~~ provided. Nucleic acid molecules that encode a single-chain protease domain or catalytically active portion thereof and also those that encode the full-length CVSP16 are provided. Also provided are nucleic acid molecules that hybridize to such CVSP16 encoding nucleic acid along at least about 70%, 80%, 90%,

95% or more of their full length and encode a protease domain or portion thereof. Hybridization is typically performed under conditions of at least low, generally at least moderate, and often high stringency; generally the hybridizing nucleic acid hybridizes along at least about 70%, 80%, 90%, 95% of its full length at the recited stringency.

Please replace the paragraph on page 10, lines 9-18, with the following:

Additionally provided herein are antibodies that specifically bind to the CVSP16, particularly the CVSP16s provided, including CVSP16s provided herein that [[does]] do not include at least 5, 7, 10, 15, 20 or more contiguous amino acids from SEQ ID No. 21. Also provided are antibodies that specifically bind to CVSP16 proteases that contain at least two protease domains of a serine protease 16 (CVSP16) and include at least 5 contiguous amino acids corresponding to residues 508-544 of SEQ ID No. 6[[.]] or ~~contains~~ contain the contiguous sequence Asn Asp Ser or Trp Asn Asp or Ser Cys Trp Asn Asp Ser or Cys Trp Asn Asp Ser or Gln Thr His or Leu Gln Thr His in the second protease domain.

Please replace the paragraph on page 10, line 19 through page 11, line 5, with the following:

Included are antibodies that specifically bind to the protein or protease domain, including [[to]] the single and/or double chain forms thereof. Among the antibodies are two-chain-specific antibodies, and single-chain-specific antibodies and neutralizing antibodies that inhibit functional activity (*i.e.*, catalytic activity and/or substrate or binding activity). Also provided are antibodies that bind with at least 2-fold, 5-fold, 10-fold or 100-fold greater affinity to CVSP16 polypeptides that do not include a contiguous portion (5, 7, 10, 15, 20 or more amino acid residues) of the sequence of amino acids set forth in SEQ ID No. 21 compared to a CVSP polypeptide that includes SEQ ID No. 21. Typically the CVSP16 polypeptides that do not include the sequence of amino acids set forth in SEQ ID No. 21 do not include it between residues

corresponding to Q_{660} and M_{661} (see, SEQ ID No. 6) and/or the CVSP16s polypeptides contain at least two protease domains of a serine protease 16 (CVSP16) and include at least 5 contiguous amino acids corresponding to residues 508-544 of SEQ ID No. 6[[.]] or ~~contains~~ contain the contiguous sequence Asn Asp Ser or Trp Asn Asp or Ser Cys Trp Asn Asp Ser or Cys Trp Asn Asp Ser or Gln Thr His or Leu Gln Thr His in the second protease domain.[[.]]

Please replace the paragraph on page 11, lines 12-21, with the following:

Also provided are cells, combinations, kits and articles of manufacture that contain the nucleic acid encoding the CVSP16 and/or the CVSP16. Further provided herein are prognostic, diagnostic, therapeutic screening methods using CVSP16 and the nucleic acids encoding CVSP16. Also provided are transgenic non-human animals bearing inactivated genes encoding CVSP16 and bearing the genes (or inserted cDNA) encoding the CVSP16, particularly under a non-native promoter control or on an exogenous element, such as a plasmid or artificial chromosome, are additionally provided herein. Also provided are nucleic acid molecules encoding each [[of]] CVSP16 and domains thereof.

Please replace the paragraph on page 12, lines 8-18, with the following:

The CVSP16 polypeptides (including those that include all or a portion of SEQ ID No. 21) are of interest for a variety of reasons. For example, they appear to be expressed and/or activated at different levels in tumor cells from normal cells, or to have functional activity that is different in tumor cells from normal cells, such as by an alteration in a substrate therefor, or a cofactor. ~~The CVSP16 polypeptides (including those that include all or a portion of SEQ ID No. 21) are of interest for a variety of reasons. For example, they appear to be expressed and/or activated at different levels in tumor cells from normal cells, or to have functional activity that is different in tumor cells from normal cells, such as by an alteration in a substrate therefor, or a cofactor.~~

Please replace the paragraph on page 12, lines 19-25, with the following:

It is shown herein, that CVSP16 is expressed in cervical cancer. It also may be expressed in colon, breast, stomach, uterine, ovarian, lung and prostate tumors and in other tumors as well as in certain normal cells and tissues (see *e.g.*, EXAMPLES for an exemplary tissue-specific expression profile). The expression and/or activation thereof and/or its presence above a predetermined level ~~among is~~ in a body fluid can be diagnostic or prognostic of cancer.

Please replace the paragraph on page 13, lines 11-19, with the following:

Methods of diagnosing a disease or disorder characterized by detecting an aberrant level of a CVSP16 in a subject [[is]] are provided. The method can be practiced by measuring the level of the DNA, RNA, protein or functional activity of the CVSP16. An increase or decrease in the level of the DNA, RNA, protein or functional activity of the CVSP16, relative to the level of the DNA, RNA, protein or functional activity or any other suitable control, found in an analogous sample not having the disease or disorder (or other suitable control) is indicative of the presence of the disease or disorder in the subject.

Please replace the paragraph on page 14, lines 1-7, with the following:

Computer based screening methods are also provided. In these methods, interactions between simulated test compounds and computer simulated CVSP16 polypeptides are assessed, such as by computational docking or binding studies. Test compounds predicted to bind or otherwise interact with a CVSP16 polypeptide are selected as drug candidates. Further characterization and study, such as *in vitro* assays, can be performed.

Please replace the paragraph on page 14, lines 8-12, with the following:

Also provided herein are modulators of the activity of CVSP16, especially the modulators (*i.e.*, antagonists, agonists, inhibitors), including antibodies and RNA molecules, and molecules obtained according to the screening methods ~~provide~~ provided herein. Such modulators can have use in treating cancerous conditions, and other neoplastic conditions.

Please replace the paragraph on page 14, lines 13-16, with the following:

Pharmaceutical compositions containing a protease domain and/or full-length or two protease domains or other domain of a CVSP16 polypeptide are provided herein in a pharmaceutically acceptable carrier or excipient ~~are provided herein~~.

Please replace the paragraph on page 14, lines 17-25, with the following:

Also provided are articles of manufacture that contain CVSP16 polypeptide and/or a protease domain or protease domains of a CVSP16 polypeptide as single-chain zymogen and activated forms and as full-length [[form]] forms, zymogen or activated forms and other forms thereof. The articles contain a) packaging material; b) a CVSP16 polypeptide (or encoding nucleic acid), particularly a polypeptide containing a single chain protease domain thereof; and c) a label indicating that the article is for use in assays for identifying modulators of the activities of a CVSP16 polypeptide or for use in diagnostic assays.

Please replace the paragraph on page 14, line 26 through page 15, line 5, with the following:

Conjugates containing a) a CVSP16 polypeptide or protease domain in single chain [[from]] form; and b) a targeting agent linked to the SP directly or via a linker, wherein the agent facilitates: i) affinity isolation or purification of the conjugate; ii) attachment of the conjugate to a surface; iii) detection of the conjugate; or iv) targeted delivery to a selected tissue or cell, [[is]] are provided herein. The conjugate can contain a plurality of agents linked thereto. The conjugate can be a chemical conjugate; and it can be a fusion protein. Targeting agents include proteins and peptide fragments. The protein or peptide fragment can include a protein binding sequence, a nucleic acid binding sequence, a lipid binding sequence, a polysaccharide binding sequence, or a metal binding sequence.

Please replace the paragraph on page 17, line 25 through page 18, line 6 with the following:

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the invention(s) belong. All patents, patent applications, published applications and publications, Genbank sequences, databases, websites and other published materials referred to throughout the entire disclosure herein, unless noted otherwise, are incorporated by reference in their entirety. In the event that there are a plurality of definitions for terms herein, those in this section prevail. Where reference is made to a URL or other such identifier or address, it is understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet. Reference thereto evidences the availability and public dissemination of such information.

Please replace the paragraph on page 18, lines 7-11, with the following:

As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in ~~accord~~ accordance with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (see, (1972) *Biochem. 11*:942-944).

Please replace the paragraph on page 20, lines 10-21, with the following:

Thus, as used herein a protease domain of a CVSP16, whenever referenced herein, includes at least one or all of or any combination of or a catalytically active portion of a CVSP16 polypeptide as defined herein. A protease domain of a CVSP16 protein refers to a protease domain of a CVSP16 that exhibits serine proteolytic activity. Hence it is at least a minimal portion of the protein that exhibits proteolytic activity (or binds to a substrate or ligand) as a single-chain form or as an activated [[form.]] form as assessed by standard assays *in vitro*. It refers, herein, to a single chain form and also multi-chain activated forms. Exemplary protease domains include at least a sufficient

portion of a sequence of amino acids set forth in SEQ ID No. 6 (encoded by nucleotides in SEQ ID No. 5) to exhibit protease activity.

Please replace the paragraph on page 21, lines 20-26, with the following:

Exemplary of a protease domain of a CVSP16 is a polypeptide set forth as amino acids 46 to 286 or including amino acids 326 to 550, particularly 323-550, of SEQ ID No. 6, which can <u>be</u> provided as a single-chain isolated molecule or as molecule that contains both domains but not the full-length CVSP16. The single-chain form can be a zymogen or activated form in which the N-terminus corresponds to the N-terminus produced by activation cleavage.

Please replace the paragraph on page 23, lines 13-19, with the following:

There are two types of single-chain forms; active and zymogen forms. When cleaved at the activation site, there <u>results</u> only one single chain active [[forms]] <u>form</u>. Any form that results from activation cleavage or that has an N-terminus at a site that is the site of cleavage is an active single-chain [[forms]] <u>form</u>. The N-terminus of an activated form must result from activation cleavage and be at that site. Any other single-chain form, which has a different N-terminus is a zymogen.

Please replace the paragraph on page 24, lines 3-8, with the following:

d) a ~~polyceptide~~ <u>polypeptide</u> that contains at least two protease domains of a serine protease 16 (CVSP16) and includes at least 5 contiguous amino acids corresponding to residues 508-544 of SEQ ID No. 6. or contains the contiguous sequence Asn Asp Ser or Trp Asn Asp or Ser Cys Trp Asn Asp Ser or Cys Trp Asn Asp Ser or Gln Thr His or Leu Gln Thr His in the second protease domain;

Please replace the paragraph on page 24, lines 17-25, with the following:

f) the polypeptide is encoded by a sequence of nucleotides that hybridizes under conditions of at least moderate, and can be high, stringency along at least 70% of its full length to a sequence of nucleotides [[than]] <u>that</u> encodes a polypeptide of any of a)-e), wherein the polypeptide does not include

at least 5 or at least 6 or at least 7 or at least 8 contiguous or at least 9 or at least 10 contiguous amino acids from SEQ ID No. 21 up to all of SEQ ID No. 21, and particularly do not include any amino acids therefrom between amino acids corresponding to Gln_{660} and Met_{661} of SEQ ID No. 6;

Please replace the paragraph on page 25, line 29, through page 26, line 8, with the following:

The CVSP16 can be from any animal, particularly a mammal, and includes but [[are]] <u>is</u> not limited to, primates including humans, gorillas and monkeys; rodents, such as mice and rats; fowl, such as chickens; ruminants, such as goats, cows, deer, sheep; ovine, such as pigs and other animals. The full length zymogen or a multi-chain activated form is contemplated as is any domain thereof, including a protease domain, which can be a three-chain activated form, two-chain activated form, or a single chain activated or zymogen form. An exemplary CVSP16 protein includes a sequence of amino acids set forth in SEQ ID No. 6 that includes a protease domain or a catalytically active portion thereof.

Please replace the paragraph on page 27, lines 6-12, with the following:

Also contemplated are nucleic acid molecules that encode a polypeptide that has proteolytic activity in an *in vitro* proteolysis assay and that have at least 80%, 85%, 90% or 95% sequence identity with the full length of a protease domain of a CVSP16 polypeptide as provided herein, or that hybridize along at least about 70%, 80%, 90% and 95% of their full length to [[a]] nucleic acids that encode a protease domain, particularly under conditions of moderate, generally high, stringency.

Please replace the paragraph on page 28, lines 3-13, with the following:

As used herein, a two-chain form of a protease domain refers to a two-chain form that is formed from a single chain[[-]]form following activation cleavage or other cleavage of the protease. In such forms the Cys pairing between, in this instance, a Cys outside a protease domain and an ~~upaired~~

unpaired Cys in PD1 or PD2, links a protease domain to the remainder of the polypeptide and the activation cleavage cleaves the chain. A two-chain protease domain form refers to any form in which the "remainder of the polypeptide" is shortened or cleaved from the full-length and includes a Cys from outside a protease domain. The three chain form refers to any form in which two of the protease domains are activated in this manner.

Please replace the paragraph on page 30, lines 4-15, with the following:

As used herein, an anti-cancer agent (used interchangeably with "anti-tumor or anti-neoplastic agent") refers to any agents used in anti-cancer treatment. These include any agents, when used alone or in combination with other compounds, that can alleviate, reduce, ameliorate, prevent, or place or maintain in a state of remission of clinical symptoms or diagnostic markers associated with neoplastic disease, tumors and cancer, and can be used in methods, combinations and compositions provided herein. Non-limiting examples of anti-neoplastic agents include anti-angiogenic agents, alkylating agents, ~~antimetabolite~~ antimetabolites, certain natural products, platinum coordination complexes, anthracenediones, substituted ureas, methylhydrazine derivatives, adrenocortical suppressants, certain hormones, antagonists and anti-cancer polysaccharides.

Please replace the paragraph on page 41, line 25 through page 42, line 2, with the following:

As used herein, antibody fragment refers to any derivative of an antibody that is less [[then]] than full length, retaining at least a portion of the full-length antibody's specific binding ability. Examples of antibody fragments include, but are not limited to, Fab, Fab', $F(ab)_2$, single-chain Fvs (scFV), FV, dsFV diabody and Fd fragments. The fragment can include multiple chains linked together, such as by disulfide bridges. An antibody fragment generally contains at least about 50 amino acids and typically at least 200 amino acids.

Please replace the paragraph on page 43, lines 12-19, with the following:

As used herein, biological activity refers to the *in vivo* activities of a compound or physiological responses that result upon *in vivo* administration of a compound, composition or other mixture. Biological activity, thus, encompasses therapeutic effects and pharmaceutical activity of such compounds, compositions and mixtures. Biological activities can be observed in *in vitro* systems designed to test or use such activities. Thus, for purposes herein a biological activity of a protease is its catalytic activity in which a polypeptide is hydrolyzed.

Please replace the paragraph on page 48, lines 9-15, with the following:

b) antibodies: identification of a ligand-binding site on the antibody molecule that combines with the epitope of an antigen of interest can be investigated; determination of a sequence that mimics an antigenic epitope can lead to the development of vaccines of which the immunogen is based on one or more of such sequences or lead to the development of related diagnostic agents or compounds useful in therapeutic treatments such as for auto-immune diseases;

Please replace the paragraph on page 52, lines 17-29, with the following:

As used herein, a molecule, such as an antibody, that specifically binds to a polypeptide typically has a binding affinity (K_a) of at least about 10^6 l/mol, 10^7 l/mol, 10^8 l/mol, 10^9 l/mol, 10^{10} l/mol or greater and binds to a protein of interest generally with at least 2-fold, 5-fold, generally 10-fold or even 100-fold or greater, affinity than to other proteins. For example, an antibody that specifically binds to the protease domain compared to the full-length molecule, such as the zymogen form, binds with at least about 2-fold, typically 5-fold or 10-fold higher affinity, to a polypeptide that contains only the protease domain than to the zymogen form of the full-length molecule. Such specific binding also is referred to as selective binding. Thus, specific or selective binding refers to greater binding affinity (generally at least 2-fold, 5-fold, 10-fold or more) to a targeted site or locus compared to a non-targeted site or locus.

Please replace the paragraph on page 56, lines 18-25, with the following:

Provided are ~~polypeptides~~ polypeptide family members designated CVSP16. The CVSP16s provided herein are serine proteases that are expressed and/or activated in certain tumors; hence their activation or expression can serve as a diagnostic marker for tumor development, growth and/or progression. The CVSP16 polypeptides provided herein and can be used as a drug or therapeutic target and used in screening assays, including those exemplified herein. Dimerized and higher multimers of CVSP16 polypeptides and/or portions thereof are provided.

Please replace the paragraph on page 57, line 21 through page 58, line 2, with the following:

It is shown herein, that CVSP16s provided herein are expressed and/or activated in certain tumors; hence their activation or expression can serve as a diagnostic marker for tumor development, growth and/or progression. The CVSP16 also is intended for use as a drug target and used in screening assays, including those ~~CSVP16s~~ CVSP16s exemplified herein. The CVSP16 polypeptides provided herein are expressed or activated by or in tumor cells, typically at a level that differs from the level in which they are expressed by the non-tumor cell of the same type. Hence, for example, if the SP expressed by a prostate or ovarian tumor cell is to be of interest herein with respect to ovarian or prostate cancer, it should have an expression, extent of activation or activity that is different from that in non-tumor cells. CVSP16 is expressed in lung, colon, prostate, breast, uterine, ovarian and other tumor cells.

Please replace the paragraph on page 59, lines 26-31, with the following:

d) a ~~polyeptide~~ polypeptide that contains at least two protease domains of a serine protease 16 (CVSP16) and includes at least 5 contiguous amino acids corresponding to residues 508-544 of SEQ ID No. 6[[.]] or contains the contiguous sequence Asn Asp Ser or Trp Asn Asp or Ser Cys Trp Asn Asp

Ser or Cys Trp Asn Asp Ser or Gln Thr His or Leu Gln Thr His in the second protease domain;

Please replace the paragraph on page 61, lines 1-18, with the following:

Also, provided herein are isolated substantially pure polypeptides that contain a protease domain of a CVSP16. The polypeptide protein also can include other non-CVSP16 sequences of amino acids, but includes a protease domain or a sufficient portion thereof to exhibit catalytic activity (or other functional activity, such as substrate or ligand binding activity) in any *in vitro* assay that ~~assess~~ assesses such protease activity, such as any provided herein. The CVSP16 polypeptides do not include the sequence of amino acids set forth in SEQ ID No. 21 and/or they do not include at least 5, 7, 9, 10, 11, 15, 20 or more contiguous amino acids thereof between amino acids that correspond to [[Q660]]Q_{660} and [[M661]]M_{661} of SEQ ID No. 6 and/or the CVSP16 polypeptide contains at least two protease domains of a serine protease 16 (CVSP16) and includes at least 5 contiguous amino acids corresponding to residues 508-544 of SEQ ID No. 6[[.]] (SEQ ID No. 22) or contains the contiguous sequence Asn Asp Ser or Trp Asn Asp or Ser Cys Trp Asn Asp Ser or Cys Trp Asn Asp Ser or Gln Thr His or Leu Gln Thr His in the second protease domain. Such polypeptides are zymogens or activated single-, two-, or three-chain molecules.

Please replace the paragraph on page 61, line 26, through page 62, line 11, with the following:

Also provided is a substantially purified protein including a sequence of amino acids that has at least 60%, 70%, 80%, 90% or about 95%, identity to the exemplified CVSP16 or to a protease domain thereof, and does not include at least 5, 7, 9, 11, 15, 20 or more contiguous amino acids of SEQ ID No. 21. Percentage identity is determined using standard algorithms and gap penalties that maximize the percentage identity. A [[huma]] human CVSP16 polypeptide is exemplified, although other ~~mammalia~~ mammalian CVSP16 polypeptides are contemplated and are obtained by standard methods using the disclosed

CVSP16-encoding nucleic acid (or antibodies made to the CVSP16) to isolate corresponding nucleic acid molecules (and/or CVSP16s) from other species. Polypeptides or peptides encoded by splice variants of the exemplified encoding nucleic acid (SEQ ID No. 5), particularly those with a proteolytically active protease domain, but not containing at least 5, 7, 10, 15, 20 or more contiguous amino acids from SEQ ID No. 21, particularly inserted between the amino acids corresponding to [[Q660]]Q_{660} and [[M661]]M_{661} (SEQ ID No. 6) are provided.

Please replace the paragraph on page 62, lines 12-26, with the following:

Provided are substantially purified CVSP16 polypeptides and functional domains thereof, including catalytically active domains and portions, that have at least about 60%, 70%, 80%, 90% or about 95% sequence identity with a CVSP16 that includes the sequence of amino acids set forth in SEQ ID No. 6 or a catalytically active portion thereof. The CVSP16 ~~polyeptides~~ polypeptides provided herein do not include at least 5 contiguous amino acid residues as set forth in SEQ ID No. 21, particularly between residues corresponding to Q_{660} and M_{661} of SEQ ID No. 6. Also provided are polypeptides that are encoded by the nucleic acid molecules provided herein. Polypeptides that contain at least two protease domains of a serine protease 16 (CVSP16) and ~~includes~~ include at least 5 contiguous amino acids corresponding to residues 508-544 of SEQ ID No. 6[[.]] or ~~contains~~ contain the contiguous sequence Asn Asp Ser or Trp Asn Asp or Ser Cys Trp Asn Asp Ser or Cys Trp Asn Asp Ser or Gln Thr His or Leu Gln Thr His in the second protease domain.

Please replace the paragraph on page 65, lines 1-6, with the following:

CVSP16 has two protease domains PD1 and PD2 (see, *e.g.*, amino acids 46 to 286 [[an]] and amino acids 323 to 550 of SEQ ID No. 6, respectively). Polypeptides that contain PD1 or PD2 as the only CVSP16 portion thereof ~~are provided~~ or that contain PD1 and PD2 but do not include at least 5, 7, 10, 15, 20 or more contiguous amino acids of SEQ ID No. 21 are provided.

Please replace the paragraph on page 66, lines 2-19, with the following

Antigenic epitopes that contain at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 40, 50, and typically 10-15 amino acids of the CVSP16 polypeptide are provided. These antigenic epitopes are used, for example, to raise antibodies. Antibodies, see further discussion below, specific for each epitope or combinations thereof are also provided. Also provided are antibodies that bind with at least 10-fold or 100-fold greater affinity to CVSP16 polypeptides that do not include the sequence of amino acids set forth in SEQ ID No. 21 (particularly do not include any amino acids therefrom between amino acids corresponding to Gln_{660} and Met_{661} of SEQ ID No. 6) compared to those that include SEQ ID No. 21. In particular, provided are antibodies that bind to a CVSP16 polypeptide provided herein that does not include at least 5, 7, 9, 10, 15, 20 contiguous amino acids of SEQ ID No. 21, particularly where the contiguous amino acids are inserted between amino acids corresponding to Q_{660} and M_{661}, with at least 2-, 5-, 10-, 100-fold greater affinity than to a polypeptide that includes the at least 5 contiguous amino acids set forth in SEQ ID No. 21, particularly where the continuous amino acids are inserted between amino acids corresponding to Q_{660} and M_{661}.

Please replace the paragraph on page 66, line 21, through page 67, line 22, with the following:

Full-length CVSP16, zymogen and activated forms thereof and CVSP16 protease domains, portions thereof, and muteins and derivatives of such polypeptides are provided. Among the derivatives are those based on animal CVSP16s, including, but are not limited to, rodent, such as mouse and rat; fowl, such as chicken; ruminants, such as goats, cows, deer, sheep; ovine, such as pigs; and humans. For example, CVSP16 derivatives can be made by altering their sequences by substitutions, additions or deletions. CVSP16 derivatives include, but are not limited to, those containing, as a primary amino acid sequence, all or part of the amino acid sequence of CVSP16, including altered

sequences in which functionally equivalent amino acid residues are substituted for residues within the sequence resulting in a silent change. For example, one or more amino acid residues within the sequence can be substituted by another amino acid of a similar polarity which acts as a functional equivalent, resulting in a silent alteration. Substitutes for an amino acid within the sequence can be selected from other members of the class to which the amino acid belongs. For example, the nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine. The polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine. The positively charged (basic) amino acids include arginine, lysine and histidine. The negatively charged (acidic) amino acids include aspartic acid and glutamic acid (see, *e.g.*, Table 1). Muteins of the CVSP16 or a domain thereof, such as a protease domain, in which up to about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90% or 95% of the amino acids are replaced with another amino acid are provided. Generally such muteins retain at least about 1%, 2%, 3,%, 5%, 7%, 8%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or more (or in increased activity, *i.e.*, 101%, 102%, 103%, 104%, 105%, 110% or greater) of the protease activity of the unmutated protein. Those of skill in the art recognize that a polypeptide that retains at least 1% of the activity of the wild-type protease is sufficiently active for use in screening assays or in other applications.

Please replace the paragraph on page 70, line 30, through page 71, line 4, with the following:

g) the polypeptide has at least 60%, 70%, 80%, 90% or about 95% sequence identity with a polypeptide of any of a)-f), where the polypeptide does not include at least about 5, 6, 7, 8, 9, 10, 15 or 20 contiguous amino acids from SEQ ID No. 21 up to all of SEQ ID No. 21, and particularly do not include any amino acids therefrom between amino acids corresponding to Gln_{660} and Met_{661} of SEQ ID No. 6; and/or

Please replace the paragraph on page 71, lines 5-19, with the following:

h) a polypeptide encoded by a splice variant of a sequence of nucleotides that encodes a CVSP16 polypeptide, including a polypeptide of any of a)-f) as long as the resulting polypeptide ~~the polypeptide~~ does not include at least about 5, 6, 7, 8, 9, 10, 15 or 20 contiguous amino acids from SEQ ID No. 21 up to all of SEQ ID No. 21, and particularly does not include any amino acids therefrom between amino acids corresponding to Gln_{660} and Met_{661} of SEQ ID No. 6 and/or the polypeptide encoded by the splice variant contains at least two protease domains of a serine protease 16 (CVSP16) and includes at least 5 contiguous amino acids corresponding to residues 508-544 of SEQ ID No. 6[[.]] or contains the contiguous sequence Asn Asp Ser or Trp Asn Asp or Ser Cys Trp Asn Asp Ser or Cys Trp Asn Asp Ser or Gln Thr His or Leu Gln Thr His in the second protease domain. Smaller nucleic acid molecules that encode polypeptides that retain protease activity as single chains or as other truncated single-chain forms are provided.

Please replace the paragraph on page 72, line 23, through page 73, line 2, with the following:

In an exemplary embodiment, a nucleic acid molecule that encodes a CVSP16 polypeptide is provided. In particular, an encoding nucleic acid molecule with an open reading frame within the sequence of nucleotides set forth in SEQ ID No. 5 is provided. The encoded protein is set forth in SEQ ID NO. 6 (see, also EXAMPLE 1). Also provided [[a]]<u>are</u> nucleic acid molecules that encode the mature polypeptide (residues 24-752) and one or both protease domains. The encoded polypeptide does not include at least about 5, 6, 7, 8, 9, 10, 15 or 20 contiguous amino acids from SEQ ID No. 21 up to all of SEQ ID No. 21, and particularly do not include any amino acids therefrom between amino acids corresponding to Gln_{660} and Met_{661} of SEQ ID No. 6.

Please replace the paragraph on page 73, line 24, through page 74, line 2, with the following:

The isolated nucleic acids can include at least 8 nucleotides of a CVSP16-encoding sequence. In other embodiments, the nucleic acids can contain at least 10, 14, 16, 50, 100 nucleotides, 150 nucleotides, or 200 nucleotides of a CVSP16-encoding sequence provided that the nucleic acid molecules ~~includes~~ include codons encoding [[Q660]]$\underline{Q_{660}}$ and [[M661]]$\underline{M_{661}}$ as contiguous amino acids, ~~particular~~ particularly those encoding amino acids 655-665 or smaller portions thereof that include Q_{660} and M_{661} of SEQ ID No. 6. The nucleic acid molecules generally include ~~sequence~~ sequences of nucleotides that encode residues that correspond to Q_{660} and M_{661} of SEQ ID No. 6.

Please replace the paragraph on page 74, lines 9-20, with the following:

Also provided are fragments thereof or oligonucleotides that can be used as probes or primers and that contain at least about 10, 14, 16 nucleotides, generally less than 1000 or less than or equal to 100, set forth in SEQ ID No. 5 (or the complement thereof), particularly those that span [[nt.]] nucleotides 1978-1983; or contain at least about 30 nucleotides (or the complement thereof) or contain oligonucleotides that hybridize along their full length (or at least about 70%, 80% or 90% thereof) to any such fragments or oligonucleotides. The length of the fragments are a function of the purpose for which they are used and/or the complexity of the genome of interest. Generally probes and primers contain less than about 500, 150, 100 nucleotides.

Please replace the paragraph on page 79, lines 7-31, with the following:

Once the DNA fragments are generated, identification of the specific DNA fragment containing the desired gene can be accomplished in a number of ways. For example, a portion of the SP protein (of any species) gene (*e.g.*, a PCR amplification product obtained as described above or an oligonucleotide having a sequence of a portion of the known nucleotide sequence) or its specific RNA, or a fragment thereof can be purified and labeled, and the generated DNA fragments can be screened by nucleic acid hybridization to the labeled probe (Benton and Davis, *Science 196*:180 (1977); Grunstein and Hogness, *Proc.*

Natl. Acad. Sci. U.S.A. 72:3961 (1975)). Those DNA fragments with substantial homology to the probe hybridize. It also is possible to identify the appropriate fragment by restriction enzyme digestion(s) and comparison of fragment sizes with those expected according to a known restriction map if such is available or by DNA sequence analysis and comparison to the known nucleotide sequence of SP protein. Further selection can be carried out on the basis of the properties of the gene. Alternatively, the presence of the gene can be detected by assays based on the physical, chemical, or immunological properties of its expressed product. For example, cDNA clones, or DNA clones which hybrid-select the proper mRNA, can be selected which produce a protein that, *e.g.*, has similar or identical electrophoretic migration, isoelectric focusing behavior, proteolytic digestion maps, antigenic properties, serine protease activity. If an anti-SP protein antibody is available, the protein can be identified by binding of labeled antibody to the ~~putatively~~ putative SP protein synthesizing clones, in an ELISA (enzyme-linked immunosorbent assay)-type procedure.

Please replace the paragraph on page 92, lines 14-23, with the following:

For example, in practicing such methods the CVSP16 polypeptide is mixed with a potential binding partner or an extract or fraction of a cell under conditions that allow the association of potential binding partners with the polypeptide. After mixing, peptides, polypeptides, proteins or other molecules that have become associated with a CVSP16 are separated from the mixture. The binding partner that bound to the CVSP16 can then be removed and further analyzed. To identify and isolate a binding partner, the entire protein, for instance the entire disclosed protein of SEQ ID [[Nos.]]NO: 6 can be used. Alternatively, a fragment of the protein can be used.

Please replace the paragraph on page 95, lines 1-2, with the following:

4. Methods for Identifying Agents that Modulate the Expression of a Nucleic Acid Encoding a CVSP16

Please replace the paragraph on page 98, lines 14-23, with the following:

Anti-peptide antibodies can be generated using synthetic peptides corresponding to, for example, the carboxy terminal amino acids of the CVSP16. Synthetic peptides can be as small as 1-3 amino acids in length, generally at least 4 or more amino acid residues long. The peptides can be coupled to KLH using standard methods and can be immunized into animals, such as rabbits or ungulate. Polyclonal antibodies then can [[then]] be purified, for example using Actigel beads containing the covalently bound peptide, or other reagents for affinity purification methods or by purifying all of the IgGs, using Protein A or Protein G columns or other such methods.

Please replace the paragraph on page 100, lines 2-12, with the following:

Although the above-described assay can be conducted where a single CVSP16 polypeptide is screened, and/or a single test substance is screened in one assay, the assay typically is conducted in a high throughput screening mode, *i.e.*, a plurality of the SP proteins are screened against, and/or a plurality of the test substances are screened simultaneously (*See generally, High Throughput Screening: The Discovery of Bioactive Substances* (Devlin, Ed.) Marcel Dekker, 1997; Sittampalam *et al.*, *Curr. Opin. Chem. Biol.*, *1*:384-91 (1997); and Silverman *et al.*, *Curr. Opin. Chem. Biol.*, *2*:397-403 (1998)). For example, the assay can be conducted in a multi-well (*e.g.*, 24-, 48-, 96-, 384-, 1536-well or higher density), chip or array format.

Please replace the paragraph on page 105, lines 20-25, with the following:

In vivo experimental models designed to evaluate the inhibitory potential of [[a]] test serine protease inhibitors, using a tumor cell line F3II known to be highly invasive (see, *e.g.*, Alonso *et al.*, *Breast Canc. Res. Treat. 40*:209-223 (1996)) can be used. Alonso describes *in vivo* studies for toxicity determination, tumor growth, invasiveness, spontaneous metastasis, experimental lung metastasis, and an angiogenesis assay.

Please replace the paragraph on page 106, line 24, through page 109, line 27, with the following:

Compounds for screening can be serine protease inhibitors, which can be tested for their ability to inhibit the activity of a CVSP16.

Exemplary serine protease inhibitors for use in the screening assays include, but are not limited to: Serine Protease Inhibitor 3 (SPI-3) (Chen, *et al. Cytokine, 11*:856-862 (1999)); Aprotinin (Iijima, R., *et al., J. Biochem. (Tokyo) 126*:912-916 (1999)); Kazal-type serine protease inhibitor-like proteins (Niimi, *et al. Eur. J. Biochem., 266*:282-292 (1999)); Kunitz-type serine protease inhibitor (Ravichandran, S., *et al., Acta Crystallogr. D. Biol. Crystallogr., 55*:1814-1821 (1999)); Tissue factor pathway inhibitor-2/Matrix-associated serine protease inhibitor (TFPI-2/MSPI), (Liu, Y. *et al. Arch. Biochem. Biophys. 370*:112-8 (1999)); Bukunin (Cui, C.Y. *et al. J. Invest. Dermatol. 113*:182-8 (1999)); ~~Nafmostat~~Nafamostat mesilate (Ryo, R. *et al. Vox Sang. 76*:241-6 (1999)); TPCK (Huang *et al. Oncogene 18*:3431-3439 (1999)); A synthetic cotton-bound serine protease inhibitor (Edwards *et al. Wound Repair Regen. 7*:106-18 (1999)); FUT-175 (Sawada, M. *et al. Stroke 30*:644-50 (1999)); Combination of serine protease inhibitor FUT-0175 and thromboxane synthetase inhibitor OKY-046 (Kaminogo *et al. Neurol. Med. Chir. (Tokyo) 38*:704-8; discussion 708-9 (1998)); The rat serine protease inhibitor 2.1 gene (LeCam, A., *et al., Biochem. Biophys. Res. Commun., 253*:311-4 (1998)); A new intracellular serine protease inhibitor expressed in the rat pituitary gland complexes with granzyme B (Hill *et al. FEBS Lett. 440*:361-4 (1998)); 3,4-Dichloroisocoumarin (Hammed *et al. Proc. Soc. Exp. Biol. Med., 219*:132-7 (1998)); LEX032 (Bains *et al. Eur. J. Pharmacol. 356*:67-72 (1998)); N-tosyl-L-phenylalanine chloromethyl ketone (Dryjanski *et al. Biochemistry 37*:14151-6 (1998)); Mouse gene for the serine protease inhibitor neuroserpin (P112) (Berger *et al. Gene, 214*:25-33 (1998)); Rat serine protease inhibitor 2.3 gene (Paul *et al. Eur. J. Biochem. 254*:538-46 (1998)); Ecotin (Yang *et al. J. Mol. Biol. 279*:945-57 (1998)); A 14 kDa plant-

related serine protease inhibitor (Roch *et al. Dev. Comp. Immunol. 22*(1):1-12 (1998)); Matrix-associated serine protease inhibitor TFPI-2/33 kDa MSPI (Rao *et al. Int. J. Cancer 76*:749-56 (1998)); ONO-3403 (Hiwasa *et al. Cancer Lett. 126*:221-5 (1998)); Bdellastasin (Moser *et al. Eur. J. Biochem. 253*:212-20 (1998)); Bikunin (Xu *et al. J. Mol. Biol. 276*:955-66 (1998)); Nafamostat mesilate (Mellgren *et al. Thromb. Haemost. 79*:342-7 (1998)); The growth hormone dependent serine protease inhibitor, Spi 2.1 (Maake *et al. Endocrinology 138*:5630-6 (1997)); Growth factor activator inhibitor type 2, a Kunitz-type serine protease inhibitor (Kawaguchi *et al. J. Biol. Chem., 272*:27558-64 (1997)); Heat-stable serine protease inhibitor protein from ovaries of the desert locust, Schistocerga gregaria (Hamdaoui *et al. Biochem. Biophys. Res. Commun. 238*:357-60 (1997)); Human placental Hepatocyte growth factor activator inhibitor, a Kunitz-type serine protease inhibitor (Shimomura *et al. J. Biol. Chem. 272*:6370-6 (1997)); FUT-187, oral serine protease inhibitor (Shiozaki *et al. Gan To Kaguku Ryoho*, 23(14): 1971-9 (1996)); Extracellular matrix-associated serine protease inhibitors (Mr 33,000, 31,000, and 27,000 (Rao, C.N., *et al., Arch. Biochem. Biophys., 335*:82-92 (1996)); An irreversible isocoumarin serine protease inhibitor (Palencia, D.D., *et al., Biol. Reprod., 55*:536-42 (1996)); 4-(2-aminoethyl)-benzenesulfonyl fluoride (AEBSF) (Nakabo *et al. J. Leukoc. Biol. 60*:328-36 (1996)); Neuroserpin (Osterwalder, T., *et al., EMBO J. 15*:2944-53 (1996)); Human serine protease inhibitor alpha-1-antitrypsin (Forney *et al. J. Parasitol.. 82*:496-502 (1996)); Rat serine protease inhibitor 2.3 (Simar-Blanchet, A.E., *et al., Eur. J. Biochem., 236*:638-48 (1996)); Gebaxate mesilate (parodi, F., *et al., J. Cardiothorac. Vasc. Anesth. 10*:235-7 (1996)); Recombinant serine protease inhibitor, CPTI II (Stankiewicz, M., *et al., (Acta Biochim. Pol. 43(3)*:525-9 (1996)); A cysteine-rich serine protease inhibitor (Guamerin II) (Kim, D.R., *et al., J. Enzym. Inhib., 10*:81-91 (1996)); diisopropylfluorophosphate (Lundqvist, H., *et al., Inflamm. Res. 44(12)*:510-7 (1995)); Nexin 1 (Yu, D.W., *et al., J. Cell Sci. 108(Pt*

12):3867-74 (1995)); LEX032 (Scalia, R., *et al., Shock 4(4)*:251-6 (1995)); Protease nexin I (Houenou, L.J., *et al., Proc. Natl. Acad. Sci. U.S.A. 92(3)*:895-9 (1995)); Chymase-directed serine protease inhibitor (Woodard S.L., *et al., J. Immunol. 153(11)*:5016-25 (1994)); N-alpha-tosyl-L-lysyl-chloromethyl ketone (TLCK) (Bourinbaiar, A.S., *et al., Cell Immunol. 155(1)*:230-6 (1994)); Smpi56 (Ghendler, Y., *et al., Exp. Parasitol. 78(2)*:121-31 (1994)); Schistosoma haematobium serine protease inhibitor (Blanton, R.E., *et al., Mol. Biochem. Parasitol. 63(1)*:1-11 (1994)); Spi-1 (Warren, W.C., *et al., Mol. Cell Endocrinol. 98(1)*:27-32 (1993)); TAME (Jessop, J.J., *et al., Inflammation 17(5)*:613-31 (1993)); Antithrombin III (Kalaria, R.N., *et al., Am. J. Pathol. 143(3)*:886-93 (1993)); FOY-305 (Ohkoshi, M., *et al., Anticancer Res. 13(4)*:963-6 (1993)); Camostat mesilate (Senda, S., *et al., Intern. Med. 32(4)*:350-4 (1993)); Pigment epithelium-derived factor (Steele, F.R., *et al., Proc. Natl. Acad. Sci. U.S.A. 90(4)*:1526-30 (1993)); Antistasin (Holstein, T.W., *et al., FEBS Lett. 309(3)*:288-92 (1992)); the vaccinia virus K2L gene encodes a serine protease inhibitor (Zhou, J., *et al., Virology 189(2)*:678-86 (1992)); Bowman-Birk serine-protease inhibitor (Werner, M.H., *et al., J. Mol. Biol. 225(3)*:873-89 (1992); FUT-175 (Yanamoto, H., *et al., Neurosurgery 30(3)*:358-63 (1992)); FUT-175; (Yanamoto, H., *et al., Neurosurgery 30(3)*:351-6, discussion 356-7 (1992)); PAI-I (~~Yreadwell~~Treadwell, B.V., *et al., J. Orthop. Res. 9(3)*:309-16 (1991)); 3,4-Dichloroisocoumarin (Rusbridge, N.M., *et al., FEBS Lett. 268(1)*:133-6 (1990)); Alpha 1-antichymotrypsin (Lindmark, B.E., *et al., Am. Rev. Respir. Des. 141(4 Pt 1)*:884-8 (1990)); P-toluenesulfonyl-L-arginine methyl ester (TAME) (Scuderi, P., *J. Immunol., 143(1)*:168-73 (1989)); Alpha 1-antichymotrypsin (Abraham, C.R., *et al. Cell 52(4)*:487-501 (1988)); Contrapsin (Modha, J., *et al., Parasitology 96 (Pt 1)*:99-109 (1988)); Alpha 2-antiplasmin (Holmes, W.E., *et al., J. Biol. Chem. 262(4)*:1659-64 (1987)); 3,4-dichloroisocoumarin (Harper, J.W., *et al., Biochemistry 24(8)*:1831-41 (1985)); Diisopropylfluorophosphate (Tsutsui, K., *et al., Biochem. Biophys. Res. Commun. 123(1)*:271-7 (1984));

Gabexate mesilate (Hesse, B., *et al., Pharmacol. Res. Commun. 16(7)*:637-45 (1984)); Phenyl methyl sulfonyl fluoride (Dufer, J., *et al., Scand. J. Haematol. 32(1)*:25-32 (1984)); Protease inhibitor CI-2 (McPhalen, C.A., *et al., J. Mol. Biol. 168(2)*:445-7 (1983)); Phenylmethylsulfonyl fluoride (Sekar *et al., Biochem. Biophys. Res. Commun., 89(2)*:474-8 (1979)); PGE1 (Feinstein *et al., Prostaglandins 14(6)*:1075-93 (1977)).

Please replace the paragraph on page 110, line 23, through page 111, line 8, with the following:

The libraries fall into roughly three categories: fusion-protein-displayed peptide libraries in which random peptides or proteins are presented on the surface of phage particles or proteins expressed from plasmids; support-bound synthetic chemical libraries in which individual compounds or mixtures of compounds are presented on insoluble matrices, such as resin beads (*see, e.g.*, Lam *et al., Nature 354*:82-84 (1991)) and cotton supports (*see, e.g.*, Eichler *et al., Biochemistry 32*:11035-11041 (1993)); and methods in which the compounds are used in solution (*see, e.g.*, Houghten *et al., Nature 354*:84-86 (1991); Houghten *et al., BioTechniques 313*:412-421 (1992); and Scott *et al., Curr. Opin. Biotechnol. 5*:40-48 (1994)). There are numerous examples of synthetic peptide and oligonucleotide combinatorial libraries and there are many methods for producing libraries that contain non-peptidic small organic molecules. Such libraries can be based on a [[basis]] <u>basic</u> set of monomers that are combined to form mixtures of diverse organic molecules or that can be combined to form a library based upon a selected pharmacophore monomer.

Please replace the paragraph on page 116, lines 13-20, with the following:

Antibodies, including polyclonal and monoclonal antibodies, that specifically bind to a CVSP16 polypeptide provided herein, including antibodies to single chain protease domains thereof, or to activated forms of a single-chain protease domain, or to full-length ~~activaed~~ <u>activated</u> or zymogen forms of the polypeptide or to other portions of a CVSP16 are provided. Generally, the

antibody is a monoclonal antibody, and typically the antibody specifically binds to a protease domain of the CVSP16 polypeptide.

Please replace the paragraph on page 116, lines 21-25, with the following:

Provided are antibodies that specifically bind to any domain of CVSP16, and antibodies that specifically bind to two-chain and/or three-chain forms thereof. Also provided are antibodies that specifically bind to an active site or active site cleft of zymogen and activated forms. Neutralizing antibodies are also provided.

Please replace the paragraph on page 116, line 26, through page 117, line 3, with the following:

The CVSP16 polypeptide and domains, fragments, homologs and derivatives thereof can be used as immunogens to generate antibodies that specifically bind CVSP16 polypeptides and portions thereof. Such antibodies include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, Fab fragments, and a Fab expression library. In a specific embodiment, antibodies to human CVSP16 polypeptide are produced. In another embodiment, complexes formed from fragments of CVSP16 polypeptide, [[which]] fragments which contain the serine protease domain, are used as immunogens for antibody production.

Please replace the paragraph on page 117, lines 4-13, with the following:

Antibodies provided herein include, but are not limited to, monoclonal and polyclonal antibodies. They include antibodies that ~~inhibits~~ inhibit catalytic activity of a CVSP16 polypeptide provided herein and/or a ligand or substrate binding activity of the polypeptide. Also included are antibodies that specifically bind to a single-chain protease domain 1 (PD1) of a CVSP16 polypeptide and/or two-chain PD1 ~~and antibodies~~ and antibodies that specifically bind to a single-chain protease domain [[1]]2 (PD2) of a CVSP16 polypeptide and/or two chain PD2. Included are antibodies that specifically [[that]] bind to a single-chain form and/or [[to]] two-chain and/or three-chain forms of a CVSP16 polypeptide.

Please replace the paragraph on page 123, lines 23-29, with the following:

Those skilled in the art appreciate that modifications can be made to the peptides and peptide mimetics without deleteriously ~~effecting~~ affecting the biological or functional activity of the peptide. Further, the skilled artisan would know how to design non-peptide structures in three dimensional ~~terms,~~ terms that mimic the peptides that bind to a target molecule, *e.g.*, a CVSP16 polypeptide or, generally, the protease domain of CVSP16 polypeptides (see, *e.g.*, Eck and Sprang (1989) *J. Biol. Chem., 26*: 17605-18795).

Please replace the paragraph on page 124, line 25, through page 125, line 2, with the following:

Labeling of peptidomimetics usually involves covalent attachment of one or more labels, directly or through a spacer (*e.g.*, an amide group), to non-interfering position(s) on the peptidomimetic that are predicted by quantitative structure-activity data and/or molecular modeling. Such non-interfering positions generally are positions that do not form direct contacts with the ~~macromolecules(s)~~ macromolecule(s) to which the peptidomimetic binds to produce the therapeutic effect. Derivatization (*e.g.*, labeling) of peptidomimetics should not substantially interfere with the desired biological or pharmacological activity of the peptidomimetic.

Please replace the paragraph on page 134, line 23, through page 135, line 3, with the following:

Linkers [[for]] can be included in the conjugates. The conjugates can include one or more linkers between the CVSP16 polypeptide portion and the targeting agent. Additionally, linkers are used for facilitating or enhancing immobilization of a CVSP16 polypeptide or portion thereof on a solid support, such as a microtiter plate, silicon or silicon-coated chip, glass or plastic support, such as for high throughput solid phase screening protocols. Any linker known

to those of skill in the art for preparation of conjugates can be used herein. These linkers are typically used in the preparation of chemical conjugates; peptide linkers can be incorporated into fusion proteins.

Please replace the paragraph on page 135, line 23, through page 136, line 7, with the following:

Other exemplary linkers and linkages that are suitable for chemically linked conjugates include, but are not limited to, disulfide bonds, thioether bonds, hindered disulfide bonds, and covalent bonds between free reactive groups, such as amine and thiol groups. These bonds are produced using heterobifunctional reagents to produce reactive thiol groups on one or both of the polypeptides and then reacting the thiol groups on one polypeptide with reactive thiol groups or amine groups to which reactive maleimido groups or thiol groups can be attached on the other. Other linkers include, acid cleavable linkers, such as bismaleimideothoxy propane, acid labile-transferrin conjugates and adipic acid ~~diihydrazide~~ dihydrazide, that would be cleaved in more acidic intracellular compartments; cross linkers that are cleaved upon exposure to UV or visible light and linkers, such as the various domains, such as C_H1, C_H2, and C_H3, from the constant region of human IgG_1 (see, Batra *et al. Molecular Immunol. 30*:379-386 (1993)). In some embodiments, several linkers can be included in order to take advantage of desired properties of each linker.

Please replace the paragraph on page 139, lines 9-15, with the following:

Plasmids for replication and vectors for expression that contain the above nucleic acid fragments are also provided. Cells containing the plasmids and vectors are also provided. The cells can be any suitable host including, but are not limited to, bacterial cells, yeast cells, fungal cells, plant cells, insect [[cell]] cells and animal cells. The nucleic acids, plasmids, and cells containing the plasmids can be prepared according to methods known in the art including any described herein.

Please replace the paragraph on page 144, line 24, through page 145, line 3, with the following:

In particular, such an immunoassay is carried out by a method including contacting a sample derived from a patient with an anti-CVSP16 polypeptide antibody under conditions such that specific binding can occur, and detecting or measuring the amount of any specific binding by the antibody. Such binding of antibody, in tissue sections, can be used to detect aberrant CVSP16 polypeptide localization or aberrant (*e.g.*, increased, decreased or absent) levels of CVSP16 polypeptide or aberrant activity if CVSP16 or aberrant processing of CVSP16. For example, an antibody to CVSP16 polypeptide can be used to assay in a patient tissue or serum sample for the presence of CVSP16 polypeptide where an aberrant level of CVSP16 polypeptide is an indication of a diseased condition.

Please replace the paragraph on page 145, lines 4-10, with the following:

The immunoassays which can be used include, but are not limited to, competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays and ~~proteinalso isA~~protein A immunoassays.

Please replace the paragraph on page 146, lines 22-26, with the following:

Pharmaceutical compositions containing the identified compounds that modulate the activity of a CVSP16 polypeptide are provided herein. Also provided are combinations of a compound that modulates an activity of a CVSP16 polypeptide and another treatment or compound for treatment of a neoplastic disorder, such as a chemotherapeutic compound. The CVSP16 polypeptide modulator and the anti-tumor agent can be packaged as separate compositions for administration together or sequentially or intermittently. Alternatively, they can be provided as a single composition for administration or

as two compositions for administration as a single composition. The combinations can be packaged as kits.

Please replace the paragraph on page 148, lines 25-30, with the following:

The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration can be determined empirically by testing the compounds in known *in vivo* and ~~*in vivo*~~ *in vitro* systems, such as the assays provided herein.

Please replace the paragraph on page 149, lines 6-13, with the following:

Typically a therapeutically effective dosage is contemplated. The amounts administered can be on the order of 0.001 to 1 mg/ml, including about 0.005-0.05 mg/ml and about 0.01 mg/ml, of blood volume. Pharmaceutical dosage unit forms are prepared to provide from about ~~1also ismg~~ 1 mg to about 1000 mg, including from about 10 to about 500 mg, and including about 25-75 mg of the essential active ingredient or a combination of essential ingredients per dosage unit form. The precise dosage can be empirically determined.

Please replace the paragraph on page 157, lines 3-20, with the following:

The treatment or prevention method can further include administering an anti-angiogenic treatment or agent or anti-tumor agent simultaneously with, prior to or subsequent to the CVSP16 polypeptide inhibitor, which can be any compound identified that inhibits the activity of a CVSP16 polypeptide. Such compounds include small molecule modulators, a natural product or derivative thereof, an antibody or a fragment or derivative thereof containing a binding region thereof against the CVSP16 polypeptide, an antisense nucleic acid or double-stranded RNA (dsRNA), such as RNAi, encoding a portion of the CVSP16 polypeptide (or the complement thereof), and a nucleic acid containing at least a portion of a gene encoding the CVSP16 polypeptide into which a heterologous nucleotide sequence has been inserted such that the heterologous sequence

inactivates the biological activity of at least a portion of the gene encoding the CVSP16 polypeptide, in which the portion of the gene encoding a CVSP16 polypeptide flanks the heterologous sequence to promote homologous recombination with a genomic gene (or endogenous gene) encoding a CVSP16 polypeptide. In addition, such molecules are generally less than about 1000 [[nt]] nucleotides long.

Please replace the paragraph on page 158, lines 23-28, with the following:

The CVSP16 polypeptide antisense nucleic acid generally is an oligonucleotide, typically single-stranded DNA or RNA or an analog thereof or mixtures thereof. For example, the oligonucleotide includes a sequence antisense to a portion of a [[huma]] human CVSP16 polypeptide. The oligonucleotide can be modified at any position on its structure with substituents generally known in the art.

Please replace the paragraph on page 161, lines 3-6, with the following:

The antisense nucleic acids include sequence complementary to at least a portion of an RNA transcript of a CVSP16 polypeptide gene, including a [[huma]] human CVSP16 polypeptide gene. Absolute complementarily is not required.

Please replace the paragraph on page 163, lines 1-9, with the following:

RNAi can be used to inhibit expression *in vitro* or *in vivo*. Regions include at least about 21 (or 21) nucleotides that are selective (i.e. unique) for CVSP16 and are used to prepare the RNAi. Smaller fragments of about 21 nucleotides can be transformed directly (*i.e.*, *in vitro* or *in vivo*) into cells; larger RNAi dsRNA molecules are generally introduced using vectors that encode them. dsRNA molecules are at least about 21 bp long or longer, such as 50, 100, 150, 200 and longer. Methods, reagents and protocols for introducing nucleic acid molecules in to cells *in vitro* and *in vivo* are known to those of skill in the art.

Please replace the paragraph on page 163, lines 11-22, with the following:

In an exemplary embodiment, nucleic acids that include a sequence of nucleotides encoding a CVSP16 polypeptide or functional domains or ~~derivative~~ derivatives thereof, are administered to promote CVSP16 polypeptide function, by way of gene therapy. In this embodiment, the nucleic acid produces an encoded protein (or the nucleic acid or encoded RNA) that mediates a therapeutic effect by promoting CVSP16 polypeptide function. Any of the methods for gene therapy available in the art can be used (see, Goldspiel *et al.*, *Clinical Pharmacy 12*:488-505 (1993); Wu and Wu, *Biotherapy 3*:87-95 (1991); Tolstoshev, *An. Rev. Pharmacol. Toxicol. 32*:573-596 (1993); Mulligan, *Science 260*:926-932 (1993); and Morgan and Anderson, *An. Rev. Biochem. 62*:191-217 (1993); *TIBTECH 11(5)*:155-215 (1993).

Please replace the paragraph on page 167, lines 7-15, with the following:

Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include, but are not limited to, epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as ~~T also islymphocytes, B[also is]lymphocytes,~~ T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, *e.g.*, such as stem cells obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, and other sources thereof.

Please replace the paragraph on page 169, lines 4-17, with the following:

A method for treating tumors is provided. The method is practiced by administering a prodrug that is cleaved at a specific site by a CVSP16 to release an active drug or a precursor that can be converted to active drug *in vivo*. Upon contact with a cell that expresses CVSP16 activity, the prodrug is converted into an active drug. The prodrug can be a conjugate that contains the active agent, such as an anti-tumor drug, such as a cytotoxic agent, or other

therapeutic agent (TA), linked to a substrate for the targeted CVSP16, such that the drug or agent is inactive or unable to enter a cell, in the conjugate, but is activated upon cleavage. The prodrug, for example, can contain an oligopeptide, typically a relatively short, less than about 10 amino [[acids]] acid peptide, that is proteolytically cleaved by the targeted CVSP16. Cytotoxic agents, include, but are not limited to, alkylating agents, antiproliferative agents and tubulin binding agents. Others include, vinca drugs, mitomycins, bleomycins and taxanes.

Please replace the paragraph on page 169, lines 19-29, with the following:

Transgenic animal models and animals, such as rodents, including mice and rats, cows, chickens, pigs, goats, sheep, monkeys, including gorillas, and other primates, are provided herein. In particular, transgenic non-human animals that contain heterologous nucleic acid encoding a CVSP16 polypeptide or a transgenic animal in which expression of the polypeptide has been altered, such as by replacing or modifying the promoter region or other regulatory region of the endogenous gene are provided. Such an animal can [[by]] be produced by promoting recombination between endogenous nucleic acid and an exogenous CVSP16 gene that could be over-expressed or mis-expressed, such as by expression under a strong promoter, via homologous or other recombination event.

Please replace the paragraph on page 177, line 14, through page 178, line 2, with the following:

The CVSP16 and encoding nucleic acid has homology to [[a]] clones described in International PCT application No. WO 02/000860 (see SEQ ID No. 111 therein) and to clones in International PCT application No. WO 02/046383, International PCT application No. WO 01075067 and EP 1130094. The clones and predicted encoded polypeptides described in the PCT applications and EP application, however, differ from the nucleic acid molecule encoding CVSP16 polypeptides and the CVSP16 polypeptides provided herein. For example, each

of the nucleic acid molecules described in International PCT application No. WO 02/00860 includes a sequence of nucleotides encoding the sequence of amino acids set forth in SEQ ID 21 herein, and the disclosed polypeptides include the sequence of amino acids set forth in SEQ ID 21 herein. None of the polypeptides provided herein include at least 5, 10, 15, 20 or more contiguous amino acids from SEQ ID No. 21, particularly between Gln [[660]]$_{660}$ and Met [[661]]$_{661}$ (SEQ ID No. 6) or between the corresponding amino acids in other CVSP16s. Hence the CVSP16s provided herein include the sequence $Gln_{660}Met_{661}$, particularly, the contiguous sequence Gly His Gln Met Thr Ser (see, SEQ ID No. 6, amino acids 658-663). or Leu Pro Gln Gly His Gln Met Thr Ser Ala (see, SEQ ID No. 6, amino acids 655-664).

Please replace the paragraph on page 181, line 29, through page 182, line 2, with the following:

The ability of test compounds to act as inhibitors of catalytic activity of a ~~catalytic activity of a~~ CVSP16 polypeptide can be assessed in an amidolytic assay. Compound mediated inhibition of amidolytic activity of a CVSP16 ~~polyeptide~~ polypeptide or a protease domain portion thereof, can be measured by IC50 values in such an assay.

Please replace the paragraph on page 182, lines 3-19, with the following:

An exemplary assay buffer is HBSA (10 [[Mm]]mM Hepes, 150mM sodium chloride, [[Ph]]pH 7.4, 0.1% bovine serum albumin). All reagents can be purchased from Sigma Chemical Co. (St. Louis, MO), unless otherwise indicated. Two [[IC50]]IC_{50} assays at 30-minute (a 30-minute preincubation of test compound and enzyme) and at 0-minutes (no preincubation of test compound and enzyme) are conducted. For the [[IC50]]IC_{50} assay at 30-minute, the following reagents are combined in appropriate wells of a Corning microtiter plate: 50 microliters of HBSA, 50 microliters of the test compound, diluted (covering a broad concentration range) in HBSA (or HBSA alone for the uninhibited velocity measurement), and 50 microliters of the SP or protease

domain thereof diluted in buffer, yielding a final enzyme concentration of about 0.5-5 [[Nm]]nM. Following a 30-minute incubation at ambient temperature, the assay is initiated by the addition of 50 microliters of a substrate for the particular SP (see, *e.g.*, table and discussion below), which was reconstituted in deionized water, and diluted in HBSA prior to the assay, yielding a final volume of 200 microliters and a final substrate concentration of 200-600 μM.

Please replace the paragraph on page 182, lines 20-26, with the following:

For an [[IC50]]IC_{50} assay at 0-minute, the same reagents are combined: 50 microliters of HBSA, 50 microliters of the test compound, diluted (covering the identical concentration range) in HBSA (or HBSA alone for uninhibited velocity measurement), and 50 microliters of the substrate, such as a chromogenic substrate. The assay is initiated by the addition of 50 microliters of SP. The final concentrations of all components are identical in both [[IC50]]IC_{50} assays (at 30- and 0-minute incubations).

Please replace the paragraph on page 182, line 27, through page 183, line 3, with the following:

The initial velocity of the substrate hydrolysis is measured in both assays by, for example for a chromogenic substrate, the change in absorbance at a particular wavelength, using a Thermo Max® Kinetic Microplate Reader (Molecular Devices) over a 5 minute period, in which less than 5% of the added substrate was hydrolyzed. The concentration of added inhibitor, which caused a 50% decrease in the initial rate of hydrolysis was defined as the respective [[IC50]]IC_{50} value in each of the two assays (30-and 0-minute).

Please replace the paragraph on page 183, lines 16-27, with the following:

The protease domain of CVSP16 or full-length polypeptide or other catalytically active portion thereof is expressed in *Pichia pastoris*. Test compounds are screened for modulation of the activity of the CVSP16 polypeptide or portion thereof. Approximately 1-20 nM CVSP16 is mixed in

Costar 96 well tissue culture plates (Corning NY) with varying concentrations of test compounds and/or known inhibitors or ~~agonsists~~ agonists in 29.2 mM Tris, pH 8.4, 29.2 mM Imidazole, 217 mM NaCl (100 μL final volume), and allowed to incubate at room temperature for 30 minutes. 200-600 μM of a chromogenic substrate is added, and the reaction is monitored in a SpectraMAX Plus microplate reader (Molecular Devices, Sunnyvale CA) by measuring the change in absorbance at 405 nm for 30 minutes at 37°C.